REMARKS

Claims 1-9 are pending. Claims 6-7 have been withdrawn as being directed to a nonelected invention. Claim 8 has been cancelled. Claims 1-5 and 9 have been amended to clarify aspects of the claims. New claims 10-13 have been added. Accordingly, claims 1-5 and 9-13 are under consideration.

Support for amendments to claims 1-5 and 9 is presented in original claims 1-5 and 9, respectively, and in the specification. Specifically, claim 1 has been amended to correct minor typographical errors. Support for amendment to claim 5 is also found in the specification at page 7, lines 14-29, wherein the term "carrier" is described. No issue of new matter is introduced by these amendments.

Support for new claims 10-13 is found in the original claims and throughout the specification. Specifically, new claims 10-11 are supported by original claim 9. New claims 12-13 are supported by original claims 1, 4, and 5 and at page 3, lines 26-27 and page 7, lines 14-29, wherein support for the recited medicament and pharmaceutically-acceptable carrier is presented. No issue of new matter is introduced by these claims.

Applicants note that the Examiner mentioned several references in the Office Action, including: Great Britain Patent No. 2,283,239; PCT Application Nos. WO 97/44451 and WO 99/27104; and Chaplin et al. (2000) Investigative Ophthalmology and Visual Science 41:16162, as being of interest. Applicants agree with the Examiner that none of these references is deemed relevant to the method of the present invention.

Rejections under 35 USC § 112

Claims 1-5 and 8-9 have been rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 8 is cancelled herein, thereby obviating the rejection of this claim. The Examiner appears to contend that the experimental evidence presented in the specification is allegedly not sufficient to demonstrate that conjunctivitis can be prevented with the compositions of the invention. Applicants strenuously disagree with the Examiner with regard to this rejection. In view of the experimental evidence presented in the specification, which clearly demonstrates a preventative effect of histacalin protein pre-treatment for conjunctivitis induced by 48/80, and applicants' arguments hereinbelow, the

rejection of claims 1-5 and 9 is respectfully traversed.

Specifically, the Examiner has stated: *"While the specification discloses examples where a preparation comprising the claimed composition (i.e., histacalin protein) was administered to rabbits followed by challenging the rabbits with a solution of compound 48/80, there is no recitation of an example where the claimed histacalin protein was not administered and the rabbits were challenged with compound 48/80 either before dosing them with histacalin protein preparations or post administration of histacalin protein...Thus, no clear data or example is given to demonstrate that said non-infective or allergic conjunctivitis was prevented with the administration of claimed histacalin protein composition."*

Applicants respectfully assert that the Examiner's comments are not entirely clear because the Examiner acknowledges that the specification presents examples wherein histacalin is administered to rabbits and the rabbits are subsequently challenged with 48/80 and yet the Examiner has stated that there is no recitation of an example where the rabbits are challenged with 48/80 following (or prior to) administration of histacalin.

Moreover, contrary to the Examiner's position, the inventors of the present invention have presented clear and compelling evidence that histacalin pre-treatment prevents conjunctivitis. In particular, Examples 1 and 2 demonstrate that pre-treatment of rabbit eyes with histacalin prevents and/or reduces many symptoms characteristic of conjunctivitis. The efficacy of such treatment is measured qualitatively and quantitatively by reduced redness and inflammation of the eyes, two diagnostic features of conjunctivitis.

Example 1 presents results that illustrate the efficacy of various concentrations of histacalin solution in preventing conjunctivitis. Briefly, the left eye of experimental rabbits was treated topically with saline control (negative control), while the right eye of these rabbits was treated topically with 1%, 6% or 10% EV131 (histacalin). Ten minutes after treatment with either saline or histacalin, the rabbit eyes were challenged with 48/80. It is noteworthy that 48/80-mediated induction of conjunctivitis is a well accepted model system for non-infective or allergic conjunctivitis in animals, which has been used successfully to screen anti-allergic compounds to determine their efficacy. See page 9, line 28 to page 10, line 2 and reference cited therein. Thus, the experiments described in the present specification were designed to evaluate the efficacy of histacalin protein pre-treatment in prevention of conjunctivitis. The saline pre-treated eye of an experimental animal served as an internal

control with which to assess variation among individual animals in response to either histacalin pre-treatment or 48/80 induction of inflammation. In brief, a dose of 6% (2.4 mg/ml) EV131 (histacalin) conferred a significant reduction in conjunctivitis related symptoms, such as redness and inflammation of the eye. See page 10, lines 23-25. In contrast, the placebo (saline) treated eyes exhibited full blown symptoms of conjunctivitis. See page 10, line 28 to page 11, line 2. Moreover, Figure 2 clearly depicts the significant reduction in redness observed in eyes pre-treated with 6% HBP (i.e. EV131/histacalin), as compared with those treated with saline control.

In Example 2, the effect of dosing EV131 (histacalin) in the rabbit eye for eight hours prior to challenge with 48/80 was investigated. Eight rabbits were analyzed in which the right eye of each rabbit was treated with test material (EV131) and the left was treated with saline control. Eight hours following the final dose of EV131 or saline control, the eyes were challenged with 48/80. A mean reduction of 65% in eye redness was observed in EV131-treated eyes, as compared to saline treated eyes at three minutes after administration of 48/80. This result demonstrates a durable, protective (i.e., preventative) effect conferred by EV131 treatment which lasts for at least eight hours. See page 11, lines 13-15.

The Examiner has also rejected claims 1-5 and 8-9 under 35 USC § 112, first paragraph, on the grounds that the description allegedly does not enable a skilled person to administer a composition comprising a therapeutically effective amount of any or all "functional equivalent" or "active fragment" of a histacalin protein of the invention. Applicants note, however, that the Examiner acknowledges that the specification is enabled for administering a composition comprising a therapeutically effective amount of a histacalin protein, including MS-HBP1, FS-HBP1, FS-HPB2, and DRET6 protein. Claim 8 is cancelled herein, thereby obviating the rejection of this claim. Applicants deferentially disagree with the Examiner with respect to this rejection as it applies to claims 1-5 and 9 and submit that this rejection is improper for the reasons set forth below.

The specification presents ample support for what a "functional equivalent" or an "active fragment" of a protein of the invention encompasses. The term "functional equivalent" is defined on page 4, lines 18-22 as a protein which *"contains single or multiple amino-acid substitution(s), addition(s), insertion(s) and/or deletion(s) from the wild type protein sequence and/or substitutions of chemically-modified amino acids that do not affect the biological function of binding to its respective vasoactive amine"* (emphasis added). The

term "active fragment" is defined on page 4, lines 24-25 as a *"truncated protein that retains the biological function of binding to its respective vasoactive amine"* (emphasis added).

Because the terms "functional equivalent" and "active fragment" are by definition (see underlined language above) proteins which retain the biological activity of the wild type protein, then it follows that the "functional equivalents" and "active fragments" that may be employed in the present invention are useful in treating conjunctivitis. If, for example, a fragment of the histacalin protein does not retain the vasoactive amine binding properties of the histacalin protein, then the fragment will not fall within the definition of "active fragment" as used in the present application.

It is common knowledge that protein sequences may be modified to give rise to similar sequences having comparable properties. Moreover, an ordinarily skilled artisan would appreciate how such a modified protein sequence could be generated. Many approaches have been utilized to produce modified protein sequences, most of which are routine in laboratories specializing in molecular biology and/or protein chemistry. Indeed, such methods are so commonplace that the particular method by which a skilled practitioner might choose to produce a "functional equivalent" and/or an "active fragment" of a histacalin protein of the invention is rendered irrelevant when considered with respect to the functionality of any proteins produced.

An appreciation that various modifications may be made to a histacalin protein, such as MS-HBP1, FS-HBP1, FS-HBP2 or D.RET6, without compromising the biological activity of the protein is underscored by the sequence comparison shown in the specification. See Table 1, pages 5-6. The conserved residues, which are common to the histacalin family of proteins, are indicated in Table 1. A skilled artisan would be able to interpret the information presented in Table 1 and extrapolate, with a reasonable degree of success, which residues could be altered to produce a modified protein capable of binding to vasoactive amines. Moreover, the information of Table 1 also imparts considerable guidance with which a skilled practitioner could predict functionality of different fragments generated from a full length histacalin protein. The specification also provides additional guidance with regard to features required of a potential functional equivalent and/or active fragment of a histacalin protein. See page 3, line 31 to page 4, line 15.

A skilled artisan would appreciate that functionality of a modified histacalin protein (i.e., a functional equivalent) and/or a histacalin fragment could be determined with minimal

experimentation using standard vasoactive amine binding assays which are well known in the art and described in International Patent Application No. PCT/GB97/013272. Since the ability to bind vasoactive amines is a relevant feature of histacalin proteins in the context of the present invention, the preservation of this capability ensures conservation of medicinal properties.

The Examiner has also rejected claims 1-5 and 8-9 under 35 USC § 112, first paragraph, on the grounds that the description allegedly does not enable a skilled person to determine without undue experimentation what doses of a histacalin protein and/or any or all "functional equivalent" or "active fragment" of a histacalin protein would be efficacious for treating and preventing conjunctivitis. Applicants submit that ample guidance is provided in the specification with regard to appropriate dosages of therapeutic proteins of the invention. For example, the paragraph bridging pages 8 and 9 states:

> *The effective dose for a given situation can be determined by routine experimentation and is within the judgement of the skilled person. For example, in order to formulate a range of dosage values, cell culture assays and animal studies can be used. The dosage of such compounds preferably lies within the dose that is therapeutically effective in 50% of the population, and that exhibits little or no toxicity at this level. For the purposes of the present invention, an effective dose will be between 0.01 μg/kg and 50 μg/kg or, more typically, between 0.05 μg/kg and 10 μg/kg of the individual to which it is administered. Preferably, for topical administration to the eye, the histacalin proteins are present in solution at between 0.1% and 20%, more preferably between 1% and 10%. A suitable unit dose may range between 0.1μg and 1mg, preferably between 1μg and 200μg, more preferably between 10μg and 100μg for each eye. A unit dose of 96μg to each eye has been found effective.*

As indicated by the above passage, a skilled person would be able to readily identify appropriate doses from: (i) the teaching of the specification and general knowledge in the field; and/or (ii) routine experiments. The specification clearly suggests suitable doses that can be used for a histacalin protein and functional equivalents and active fragments thereof. Moreover, the skilled person would be able to "fine-tune" the appropriate dosage level using the approach described in Example 1 or using cell culture assays, for example, as suggested

on page 8, line 28. Thus, the specification not only provides considerable guidance on appropriate dosage levels but also discloses how to experimentally investigate optimal dosage levels. In short, determining an appropriate dose would be trivial to a skilled person and as such a skilled person would not be placed under any undue burden.

Claims 2-3, 5, and 8-9 have been rejected under 35 USC § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 8 has been cancelled, thereby mooting rejection of this claim. Applicants believe that claims 2-3, 5, and 9 have been amended in accordance with the Examiner's comments, thereby obviating the rejection of these claims.

In view of the above, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-5 and 9 under 35 U.S.C. §112 and withdraw the rejection of these claims.

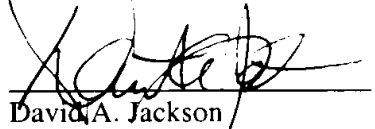
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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August 25, 2003

Attachment: Petition for a Two-Month Extension of Time